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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/756,478	01/08/2001	Jonathan S. Stamler	1818.1026-006	7552

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EXAMINER	
CHISM, BILLY D	
ART UNIT	**PAPER NUMBER**
1654	

DATE MAILED: 02/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/756,478	STAMLER ET AL.	
	Examiner	Art Unit	
	B. Dell Chism	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57* is/are pending in the application.

4a) Of the above claim(s) *35-43 and 46-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-34,44,45 and 55-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *06/25/02; 08/08/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election of Group II, in Applicants' response filed 05 November 2003, is acknowledged. Because applicant did not distinctly and specifically point out any supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

2. Claims 5-34 and 55-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 is rejected for the indefinite recitation of the phrase "effective amount" wherein it is not clear what the amount effectively does. There are no metes and bounds for the "effective amount".

Claim 15 is rejected for the indefinite recitation of the phrase "prostatic hypertrophy or restenosis". Claim 13 recites a method of treating a mammal with a disorder characterized by pathologically proliferating cells, however, being dependent on claim 13, claim 15 recites the mammal having "prostatic hypertrophy or restenosis". The recitation in claim 15 is unclear as to whether the mammal has "prostatic hypertrophy or restenosis" along with the disorder of claim 13 or if claim 15 is stating that the disorder of 13 is the "prostatic hypertrophy or restenosis". Neither condition recited in 15 is characterized by pathologically proliferating cells, per se, i.e., prostatic hypertrophy deals with size of a cell versus the amount of proliferation.

Claims 6-9, 14-17, 19-21, 23-26, 28-29, 31-34 and 56 are rejected for depending from rejected claims.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-34, 44 and 55-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims lack enablement for in vivo use of hemoproteins or enzymatically active variants thereof, either with or without reducing agents, for reduction of oxygen, treatment of cancers, tumor, pathologically proliferating cells, prostatic hypertrophy or restenosis, potentiating the cytotoxic activity of a bioreductive cytotoxic agent, enzymatically generating toxic reactive oxygen species, constricting blood vessels or sensitizing a tumor to radiation or chemotherapy.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of

experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977), have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986), and are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

The nature of the invention: The claimed invention is drawn to in vivo methods of use of hemoproteins or enzymatically active variants, either with or without reducing agents, for reduction of oxygen, treatment of cancers, tumor, pathologically proliferating cells, prostatic hypertrophy or restenosis, potentiating the cytotoxic activity of a bioreductive cytotoxic agent, enzymatically generating toxic reactive oxygen species, constricting blood vessels or sensitizing a tumor to radiation or chemotherapy.

The state of the prior art and the predictability or lack thereof in the art: Enablement must be provided by the specification unless it is well known in the art. *In re Buchner* 18 USPQ 2d 1331 (Fed. Cir. 1991). The art teaches that *Ascaris* hemoglobin (AH) functions as a

deoxygenase using nitric oxide to detoxify oxygen (Minning *et al.* 1999, Nature Vol. 401, pages 497-502), however, there is no art giving way to any predictability of in vivo uses, especially pharmaceutically (i.e., cancer treatment, vessel constriction), using AH or any other claimed hemoproteins. This lack of teachings leaves a considerable uncertainty regarding the in vivo efficacy of any hemoproteins for the claimed purposes.

The amount of direction or guidance present and the presence or absence of working examples: Given the lack of teachings found in the art regarding the in vivo therapeutic efficacy of any hemoproteins, including in vivo use of hemoproteins or enzymatically active variants, either with or without reducing agents, for reduction of oxygen, treatment of cancers, tumor, pathologically proliferating cells, prostatic hypertrophy or restenosis, potentiating the cytotoxic activity of a bioreductive cytotoxic agent, enzymatically generating toxic reactive oxygen species, constricting blood vessels or sensitizing a tumor to radiation or chemotherapy, detailed guidance is required in the specification to enable one of skill in the art to be able to use the claimed methods. This guidance is absent. The specification contains only a vague disclosure regarding various in vitro assays (pages 36-55) that show the deoxygenating ability of flavohemoglobin, *Ascaris* hemoglobin and myoglobin in chemical reactions or on dissections or cell cultures. There is no guidance as to how to make and /or use the methods commensurate with the scope of the claims. There are no working examples directed to in vivo methods of using hemoproteins or enzymatically active variants, either with or without reducing agents, for reduction of oxygen, treatment of cancers, tumor, pathologically proliferating cells, prostatic hypertrophy or restenosis, potentiating the cytotoxic activity of a bioreductive cytotoxic agent,

enzymatically generating toxic reactive oxygen species, constricting blood vessels or sensitizing a tumor to radiation or chemotherapy.

The breadth of the claims and the quantity of experimentation needed: Given the lack of teachings of predictability in the art regarding the therapeutic efficacy of any in vivo methods of using hemoproteins or enzymatically active variants, either with or without reducing agents, for reduction of oxygen, treatment of cancers, tumor, pathologically proliferating cells, prostatic hypertrophy or restenosis, potentiating the cytotoxic activity of a bioreductive cytotoxic agent, enzymatically generating toxic reactive oxygen species, constricting blood vessels or sensitizing a tumor to radiation or chemotherapy, and in the absence of sufficient guidance in applicant's disclosure to overcome the lack of teachings of predictability in the art, it would require undue experimentation by one of skill in the art to be able to use the claimed invention.

5. Claim 45 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of reducing blood flow to a mammary adenocarcinoma in a rat using flavohemoglobin, does not reasonably provide enablement for reducing blood flow to any tumor in any mammal using any hemoprotein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use

the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977), have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986), and are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

The nature of the invention: The claimed invention is drawn to in vivo methods using hemoproteins to reduce blood flow to a tumor.

The state of the prior art and the predictability or lack thereof in the art: Enablement must be provided by the specification unless it is well known in the art. *In re Buchner* 18 USPQ 2d 1331 (Fed. Cir. 1991). The art does not teach the use of hemoproteins for in vivo methods of reducing blood flow to a tumor in a mammal. The art does teach that *Ascaris* hemoglobin (AH)

functions as a deoxygenase using nitric oxide to detoxify oxygen (Minning *et al.* 1999, Nature Vol. 401, pages 497-502), however, there is no art giving way to any predictability of in vivo uses, especially pharmaceutically (i.e., cancer treatment, vessel constriction), using AH or any other claimed hemoproteins. This lack of teachings leaves a considerable uncertainty regarding the in vivo efficacy of any hemoproteins for the claimed purposes.

The amount of direction or guidance present and the presence or absence of working examples: Given the lack of teachings found in the art regarding the in vivo therapeutic efficacy of any hemoproteins, including in vivo use of hemoproteins, for reduction of blood flow to a tumor, detailed guidance is required in the specification to enable one of skill in the art to be able to use the claimed methods. This guidance is absent. The specification contains only one example for guidance, wherein flavohemoglobin is shown to reduce blood flow to a mammary adenocarcinoma in a rat (pages 53-54), however, there is no indication or data or suggestion that this is a treatment that would lead to any diminished or even to stasis of proliferating cells in vivo. There is no guidance as to how to make and /or use the methods commensurate with the scope of the claims. There are no working examples directed to in vivo methods of using any other hemoproteins for reduction of blood flow to a mammary adenocarcinoma in a rat or any other tumor or cancer in any other mammal, nor are there any examples directed to in vivo methods of using flavohemoglobin for reduction of blood flow to any other type of tumor or cancer in any other mammal, either with or without reducing agents.

The breadth of the claims and the quantity of experimentation needed: Given the lack of teachings of predictability in the art regarding the therapeutic efficacy of any in vivo methods of using hemoproteins, either with or without reducing agents, for reduction blood flow to a tumor,

and in the absence of sufficient guidance in applicant's disclosure to overcome the lack of teachings of predictability in the art, it would require undue experimentation by one of skill in the art to be able to use the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to B. Dell Chism whose telephone number is 571-272-0962. The examiner can normally be reached on 7:30 AM - 4:30 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306 for regular communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

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B. Dell Chism
06 February 2004

CHRISTOPHER R. TATE
PRIMARY EXAMINER